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Clinical features and prognostic factors affecting survival of ambulatory followed COVID-19 patients aged over 65 years

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Abstract
Aim: The majority of the patients with COVID-19 are followed ambulatory. Determination of prognostic factors of mortality in risky groups is essential to improve patient management. The aim of this study is to describe the clinical presentation in patients over 65 years of age with COVID-19 who are followed up at home by a physician and provide insights into the initial prognostic factors in this distinctive population.
Material and Methods: This is a retrospective and observational study. Clinical records of the patients aged over 65 years who were visited by the filiation team, including a physician at home, due to the diagnosis of COVID-19 disease within 2 months were reviewed. Factors affecting mortality were examined.
Results: Our study included 51 deceased (mean age: 75,1±9,0 years, 40,2% males), and 102 patients with COVID-19 who survived (mean age: 73,0±6,9 years, 68,6% male). Platelet count (< 150.000, OR 7,26, p=0,001), CRP level (< 4, OR 4,55, p=0,02), albumin level (OR 3,24, p=0,02), and Troponin I level (OR 0,03, p=0,02) were the strongest predictors for death. When propensity score matching was applied, gender (male, OR 7,14, p=0,02) and platelet count (< 150.000, OR 5,34, p=0,02) were the strongest predictors.
Discussion: Elderly COVID-19 patients have a high mortality rate. An easily measurable and accessible platelet count may be a predictor of a bad outcome. Close follow-up and timely treatment may significantly reduce mortality in high- risk elderly patients under.

Keywords
COVID-19, Frail Elderly, Ambulatory Care, Mortality

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Introduction

SARS-CoV-2 has caused a pandemic after detection of the first case in Wuhan city in December 2019. The spectrum of the disease ranges from pneumonia, mostly asymptomatic, to acute respiratory distress syndrome with a fatal outcome [1]. The first case has been reported on March 10, 2020; growth in different regions within different time periods was detected despite precautions. The case fatality rate is high in elderly patients. The case fatality rate in COVID-19 patients was 2.67% as of the end of 2020 in Turkey. Although 11% of the patients were 65 years of age or older, 72% of deaths are in this age group (available at: https://covid19.saglik.gov.tr/ COVID-19 Haftalık Durum Raporu 12/10/2020 – 18/10/2020 Türkiye).

Since the majority of the patients have mild symptoms, they are followed on an outpatient basis. However, the presence of parameters to predict worsening in patients over 65 years of age, in whom most of the mortality is seen, would enable close follow-up of this group of patients and thus reduce mortality. Although there are many studies on the prediction of mortality in elderly patients, there are no studies focused on demonstrating the deterioration of the home follow-up patient group [2,3].

The aim of this study is to describe the clinical presentation in patients aged over 65 years with COVID-19 who are followed up at home by a physician and provide insights into the initial prognostic factors in this distinctive population.

Material and Methods

Study Design

The present study was planned as a retrospective observational study. COVID-19 was diagnosed according to the guidelines of the World Health Organization (WHO) (available at: Organization WH. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance, 25 January 2020). Inclusion criteria were patients over 65 years of age who were visited by a filiation team with a physician at home due to the diagnosis of COVID-19 disease within 2 months (October 1-November 31, 2020). Exclusion criteria were those with deficient data.

This study was approved by the Ethical Review Committee of Inonu University (Ethical Review Committee decision date and number: 20/04/2021-2021/1888).

Principles of home attendants

The COVID-19 home follow-up team visited patients over 65 years who had no indication for hospitalization at home. Patients with "positive" PCR test for COVID-19 were identified and recorded daily. The population over the age of 65 was determined and their medicines were left in their homes. The planning was done so that the patient would be visited at home on the 3rd day of a positive PCR test result. Anamnesis Form and laboratory blood tubes for each patient were prepared before the visit. Each team consists of a physician, a nurse, and a driver. The physician obtained the patient history and examined the patient, the nurse measured the patient's vital findings and collected blood at home. Symptoms, past medical history, co-morbidities and current drugs of the patient were recorded. The field coordinator was contacted and referred to the hospital with an ambulance for the patients for whom the physician recommended hospitalization (impaired vital values, general condition disorder, malnutrition, elderly living alone and/or difficulty in care, etc.).

Study variables

Clinical, laboratory and radiological findings of the patients on the 3rd-day visit were obtained from the records. Parameters included in the analysis were as follows:

- Demographic and physical examination parameters: age, sex, temperature, heart rate, respiratory rate, blood pressure, peripheral oxygen saturation, comorbidities,
- Symptoms at home visit: fever, dyspnea, cough, chest pain, myalgia, fatigue, or other (including sore throat, headache, diarrhea, abdominal pain).
- Laboratory findings: total white cell blood count, lactate dehydrogenase, fibrinogen, prothrombin time, D-dimer, ferritin, C-reactive protein (CRP). Lymphocyte-monocyte-neutrophil count and percentage, RDW, MPV, NLR (Neutrophil/Lymphocyte Ratio), MLR (monocyte/lymphocyte ratio), PLR (platelet/lymphocyte ratio), troponin, albumin, triglyceride, CK, total protein

Platelet, lymphocyte count, CRP, D-dimer, Ferritin values were divided into groups according to poor prognosis criteria determined by WHO (available at: Organization WH. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance, 19 March 2020.).

Study end-points

The primary study end-point was the patient's death. Survival follow-up was assessed at 30 days after admission.

Statistical analysis

The data analysis was performed using SPSS 19.0 (Statistical Package for the Social Sciences, IBM) program. Compliance with normal distribution was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean ± standard deviation for normally distributed data, median (IQR) for non-normally distributed data, and numbers (n) and percentage (%) for countable data. The student t-test was used in the analysis of measurement data conforming to a normal distribution; the Mann-Whitney U test was used in the analysis of measurement data that did not conform to the normal distribution, and the chi-square test was used to evaluate the relationship between categorical data. Related parameters were included in the logistic regression with the "Enter" method and the estimated relative risks were calculated. D-Dimer, Lymphocyte, Platelet, Ferritin and CRP values were taken as categorical according to their prognostic cut-off for COVID-19, other continuous values were taken as categorical. To minimize the selection bias propensity, score matching applied and logistic regression was performed. The type-1 error level was accepted as 0.05.

Results

General characteristics

Fifty-one patients were included in the dead group, and 102 patients were included in the survival group. The characteristics of both groups are summarized in Table 1. Among all patients enrolled, 50.3% were female and 49.7% were male; the mean age was 73.7±7.7 years. All these patients were over 65 years of age, and 5.9% (n=6) of these were over 85 years of age. The

age average of dead patients was 75.1±9.0; 15.6% (n=8) of these are over 85 years. The age average of the patients who survived was 73.0±6.9.

There were more male patients in the group of died patients (68.6 % vs. 40.2%, x2 = 10.9, p < 0.001) than in the survivors group. Coronary Artery Disease (CAD) was more common in deceased patients (83.3%) than in survivors (16.7%) (p<0.001). When the blood groups of the patients were evaluated, A (n=65), B (n=20), 0 (n=51) and AB (n=13) blood groups did not make a significant difference between groups (p=0.621). Furthermore, Rh+ (n=129) and Rh- (n=20) blood groups did not affect the outcome in the course of the disease (p= 0.921).

Clinical manifestations

The median Pulse O2 saturation of all participants was 96 (94-97), and respiratory rate median was 18 (16-20). There was no significant difference in the proportion of patients with fever, dyspnea, chest pain, myalgia and GIS symptoms between the two groups (all P > 0.05). However, the proportion of patients with cough was significantly higher in the deceased group compared with the survivor group. While there was no difference in respiratory rate between the groups, oxygen saturation measured in room air was significantly lower in the deceased group than in the survivor group (95 (91-96) vs 96 (95-98), U = 1540, p < 0.001) (Table 1).

Laboratory findings

When the laboratory values of the COVID-19 patients in the study were examined, in the hemogram, leukocyte count, neutrophil count, neutrophil percentage, RDW-CV, NLR, MLR parameters were significantly higher in the deceased group compared to the survivor group (p<0.05). Lymphocyte count, lymphocyte percentage, monocyte percentage and platelet count were significantly lower in the deceased group (p<0.05). Total protein, triglyceride and albumin values among biochemistry parameters were significantly lower in the deceased group (p<0.05). Creatine Kinase (CK) and troponin levels were significantly higher in the deceased group than in the survival group (p<0.05). A review of serology and hormone parameters revealed that CRP and ferritin values were significantly higher in the deceased group than in thesurvivor group (p<0.05) (Table 2).

When assessing D-dimer level according to the poor prognostic factor cut-off point, there was no relationship between the disease outcome as survival or death. In the evaluation of platelet, lymphocyte count, CRP and ferritin values according to the bad prognostic factor cut-off point, the deceased group had significantly worse prognostic blood values than the survivors group (Table 2).

The variables were put into the logistic regression model with the ENTER method in order to evaluate the factors affecting the recovery or death from the disease. Nagelkerke R2 value was detected as 0.65. The specificity of the model was 80.4, the sensitivity of the model was 90.2, and the accuracy of the model was 86.9.

Survival was 7.3 times higher in patients with a platelet level above 150.000 than in those with a lower platelet level. Survival was 4.5 times higher in those with a CRP value below 4. As troponin I level decreased and albumin level increased, survival also increased significantly (Table 3).

Propensity Score Matching was applied to the groups. Survival was 7.14 times higher in men than in women. Survival was 5.34 times higher in patients with a platelet level above 150.000 than in those with a lower platelet level (Table 3).

Table 1. Demographic data and baseline clinical characteristics

Characteristics	Total (n=153)	Survival (n=102)	Dead (n=51)	Test statistic	P value (Dead vs. Survival)
Age, mean ± SD (years)	73.7±7.7	73.0±6.9	75.1±9.0	1,5	0,14
Gender, male (%)	76 (49.7)	41 (40.2)	35 (68.6)	10.9	0.001
Comorbidities n (%)					
CAD	12 (7.8)	2 (2)	10 (19.6)	14.65	<0.001
COPD	14 (9.2)	7 (6.9)	7 (13.7)	1.93	0.233
DM	38 (24.8)	25 (24.5)	13 (25.4)	0.000	1.00
Hypertension	87 (56.9)	54 (52.9)	33 (64.7)	1.469	0.226
Smoking History n (%)					
Active smoker	26 (17)	14 (13.7)	12 (23.5)	1.674	0.196
Non-smoker	127 (83)	88 (86.3)	39 (76.5)		
Symptoms n (%)					
Fever	18 (11.7)	10 (9.8)	8 (15.6)	0.638	0.425
Cough	60 (39.2)	32 (31.4)	28 (54.9)	6.94	0.008
Dyspnea	23 (15)	11 (10.8)	12 (23.5)	3.38	0.066
Chest pain	10 (6.4)	5 (4.9)	5 (9.8)	1.34	0.30
Myalgia	70 (45.8)	41 (40.2)	29 (56.9)	3.163	0.075
GIS symptoms	15 (9.8)	7 (6.9)	8 (15.7)	2.079	0.149
Loss of appetite	19 (12.4)	10 (9.8)	9 (17.6)	1.269	0.260
Vital signs					
RR, Median (IQR)	18 (16-20)	18 (16-20)	18 (15-20)	2451.5	0.55
O2 Sat, Median (IQR)	96 (94-97)	96 (95-98)	95 (91-96)	1540.0	<0.001

Continuous variables were expressed as median (interquartile range) and categorical variables were expressed as numbers (percentage). COPD, chronic obstructive pulmonary disease; CAD, Coronary Artery Disease; DM, Diabetes Mellitus; IQR, interquartile range; RR, Respiratory Rate; O2 Sat, oxygen saturation.

Table 2. The Association of Blood Analysis Values and Outcome of the Disease

Laboratory tests	Survival (n = 102)	Dead (n = 52)	p
	Median (IQR)	Median (IQR)	
Hemogram test			
White blood cell count, × $10^{9/L}$	5.08 (4.08-6.18)	6.91 (5.55-8.87)	<0.001
Lymphocyte count, × $10^{9/L}$	1.53 (1.19-1.99)	1.23 (0.85-1.61)	0.001
≤ 0.80 (n,%)	6 (35.3)	11 (64.7)	0.008
> 0,80 (n.%)	98 (70.6)	40 (29.4)	
Neutrophil count, × $10^{9/L}$	2.88 (2.07-3.64)	4.53 (3.64-6.41)	<0.001
Monocyte count, × $10^{9/L}$	0.47 (0.36-0.63)	0.56 (0.31-0.80)	0.395
RDW-CV, %	13.0 (12.4-13.9)	13.6 (12.90-15.10)	0.009
MPV, fL	10.1 (9.6-10.9)	10.2 (9.40-10.90)	0.904
NLR	1.8 (1.29-2.69)	3.81 (2.35-6.44)	<0.001
MLR	0.28 (0.21-0.44)	0.41 (0.27-0.56)	0.005
PLR	125.6 (98.11-173.43)	143.95 (90.44-230.08)	0.272
Biochemistry test			
Troponin, ng/mL	0.0 (0.0-0.1)	0.1 (0.10-0.10)	<0.001
Albumin, g/dL	3.7 (3.5-3.92)	3.4 (2.90-3.80)	0.001
Triglycerides, mg/dL	130.5 (97.75-177.00)	100.0 (62.00-139.00)	0.001
CK, U/L	77.0 (56.0-123.25)	162.8 (77.00-245.00)	<0.001
Inflammatory Markers			
Ferritin, ng/mL	186.9 (82.59-282.25)	328.8 (124.00-522.20)	0.001
≥ 500 (n.%)	7 (31.8)	15 (68.2)	<0.001
< 500	95 (72.5)	36 (27.5)	
C-reactive protein, mg/L	0.6 (0.10-2.60)	6.5 (2.57-11.38)	<0.001
≥ 4 (n.%)	17 (32.1)	36 (67.9)	<0.001
< 4 (n.%)	85 (85.0)	15 (15.0)	
Blood Coagulation test			
D-dimer, µg/mL	0.49 (0.27-0.82)	0.58 (0.39-1.12)	0.109
≥ 1 (n.%)	19 (59.4)	13 (40.6)	0.44
< 1 (n.%)	83 (68.6)	38 (31.4)	
	Mean±SD	Mean±SD	p
Hemogram test			
RDW-SD, fL	41.2±3.8	40.8±5.2	0.599
Lymphocyte %	31.4±11.8	21.5±13.8	<0.001
Monocyte %	9.7±3.4	8.1±3.7	0.015
Neutrophil %	56.9±12.2	69.7±15.5	<0.001
Platelet count, × $10^{9/L}$	199.1±56.9	175.2±69.8	0.038
≤ 150.000 (n.%)	19 (48.7)	20 (51.3)	0.01
> 150.000 (n.%)	83 (72.8)	31 (27.2)	
Biochemistry test			
Total protein, mg/dL	7.2±0.6	6.9±0.6	0.006

Discussion

In our study, we determined that a decrease in platelet count and gender are independent risk factors for mortality. We believe that thrombocytopenia detected at the beginning in outpatients should be a serious risk for mortality, and these patients should be followed carefully and closely. Since the hemogram is a simple, economical, fast and widely available laboratory test, it will ensure convenience in follow-up and applicability. According to our current knowledge, this is the first study on mortality markers in patients under outpatient follow-up.

Numerous studies have been published on mortality factors [4-7]. Age is the best known predictor of mortality, and countries with older populations have been shown to have a death-to-case ratio [4]. Our study is already focused on this high-risk group. Another frequently reported mortality predictor is the male gender. Recent studies have shown that the male gender is a risk factor independent of age [8,9]. The effect of the male gender on mortality was shown in this study, too.

We also searched for symptoms and findings in our study. Cough, shortness of breath and fever (35-40%) have been reported as main symptoms in moderate to severe disease (Available at: Organization WH. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance, 19 March 2020), [10]. However, the most common symptom (78.8-88.5%) in the early period was fever [5,8]. The most common symptoms in our patient group were myalgia, cough and fever. None of these parameters were associated with mortality. The symptoms given in the literature are usually the symptoms and signs seen in hospitalized patients. Differences from our results may be related to the fact that our patients were outpatients, the number of patients in the study and local data.

The platelet count is an ideal clinical prognostic tool because it is easy and inexpensive to perform. It is a biomarker that is independently associated with disease severity and risk of mortality in the intensive care unit [11]. Furthermore, the lower platelet count is a biomarker for disease severity scores such as the Multiple Organ Dysfunction Score (MODS), the Simplified Acute Physiology Score (SAPS) II, and the Acute Physiology and Chronic Health Assessment (APACHE) II [11]. A trend towards lower platelet counts in COVID-19 patients may suggest a worsening thrombotic state [12], lower platelet counts are associated with increased mortality. Yang et al. showed that mortality increased as the platelet count decreased (platelet counts 100–150, 50–100, and 0–50 × 109/L, respectively, and hospital mortality of 3.4 (95% confidence interval [CI] 2.4–5.0), 10.0 (95% CI), respectively) 7.2-14.0) and 13.7 (95% CI 9.9-18.9) [13]. Moreover, there are many studies showing that thrombocytopenia is associated with mortality and disease severity in line with these findings [6,7,14]. Lippi et al. stated that thrombocytopenia increased mortality 3 times in a meta-analysis including 9 studies including 1779 patients [15]. A study from Wuhan stated that thrombocytopenia detected at admission in COVID-19 patients increased mortality 4.24 times. There was a correlation with mortality was between thrombocytopenia in this study. On the contrary, improvement of thrombocytopenia in COVID-19 patients could mean imminent clinical improvement [16].

Acute phase reactants in COVID-19 infection are clinically important similar to any infection. It is also important to predict both the severity of the disease and the mortality. It may also guide the treatment decision. Several studies indicated that inflammatory markers are associated with both disease severity and mortality [17, 18]. In a meta-analysis of 64 studies on mortality and disease severity, neutrophils, lymphocytes, interleukin-6 (IL-6), ferritin, C-reactive protein (CRP), D-dimer and high sensitivity troponin I were found to be associated with mortality independent of age and gender [19]. Bannaga et al detected in hospitalized elder patients that CRP and lower serum albumin levels were associated with mortality when the age was ignored [20]. There are studies reporting that

Table 3. Evaluation of the factors affecting outcome of the disease with logistic regression in Unmatched Groups (n:153) and Matched Groups (n: 101)

Predictors	Unmatched Groups (n:153)			Matched Groups (n: 101)		
	Odds ratio	95% CI Lower-Upper	p	Odds ratio	95% CI Lower-Upper	p
Gender (Male)	2.57	0.79-8.41	0.12	7.14	1.40-36.55	0.02
CAD	0.13	0.01-1.53	0.10	0.63	0.02-18.47	0.79
Cough (present)	0.37	0.11-1.24	0.11	0.26	0.05-1.25	0.09
PulseO2	1.16	0.96-1.42	0.13	1.21	0.93-1.57	0.17
D-dimer (good prognostic)	1.19	0.33-4.28	0.79	1.91	0.36-10.13	0.45
Lymphocyte (good prognostic)	0.89	0.16-5.05	0.89	1.80	0.15-21.66	0.64
Neutrophile	0.88	0.66-1.17	0.38	0.70	0.39-1.25	0.23
Monocyte	0.86	0.41-1.81	0.69	0.90	0.46-1.76	0.76
Rdw-cv	0.75	0.75-1.02	0.07	0.77	0.49-1.22	0.26
Platelet (good prognostic)	7.26	2.15-24.56	0.001	5.34	1.26-22.66	0.02
Troponin I	0.03	0.01-0.60	0.02	0.01	0.01-1.67	0.08
Ferritin (good prognostic)	2.15	0.40-11.39	0.37	1.5	0.10-10.61	0.97
CRP (good prognostic)	4.55	1.29-16.03	0.02	5.30	0.85-33.02	0.07
Total protein	0.48	0.19-1.22	0.12	0.38	0.10-1.40	0.14
Albumin	3.24	1.17-8.94	0.02	3.24	0.93-21.09	0.06
Tg	1.002	1.00-1.01	0.33	1.1	1.00-1.02	0.08
CK	0.99	0.99-1.00	0.08	1.00	0.99-1.00	0.43

the CRP-albumin ratio and the neutrophil-albumin ratio are indicators of mortality [21, 22]. We found in our study that the inflammatory markers CRP, Troponin I and albumin were risk factors in logistic regression model but in matched groups, only thrombocytopenia and gender were independent risk factors. However, examination of inflammatory markers may also be important in predicting the clinical course.

Our study has some limitations. First, the present study was a retrospective study with a relatively small number of cases. The second is carrying out the study in a single center. These two limitations may reduce the overall reflection of the findings. These findings are preliminary data and we believe that they will guide our further studies and patient follow-ups. We think that the strength of our study is that all patients detected in a province are followed up by an outpatient doctor.

Conclusion

Our findings show that male gender and thrombocytopenia will be reliable predictors of mortality in elderly patients. Our study is the only study reporting patients followed up with an outpatient doctor without hospitalization. Since a large proportion of COVID-19 patients are followed as outpatients, our results are important in determination of follow-up parameters and predicting mortality, and may lead to larger studies.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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